Remarks

Reconsideration of this Application is respectfully requested.

The foregoing amendment to the specification is sought to correct a minor typographical error in one paragraph, and adds no new matter.

Upon entry of the foregoing amendments to the claims, claims 1-64 are pending in the application, with claims 1, 14, 22, 23, 27, 52, 57 and 62 being the independent claims. The Examiner has withdrawn claims 24, 25 and 29 from consideration. Claims 4 and 5 are amended to correct typographical errors, and claims 11, 20, 33-36 and 38 are amended to better conform to U.S. practice and/or to more particularly point out the invention as claimed. New claims 39-64 are sought to be added. Support for these amendments are found throughout the specification and claims as originally filed.

Hence, these amendments are believed to introduce no new matter, and their entry and consideration are respectfully requested.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Restriction Requirement

In response to Applicants' election of Group I, the Examiner has indicated that claims 24, 25 and 29 are withdrawn from consideration. Applicants understand that these claims may be rejoined following allowance of a claim to the compound recited in these withdrawn claims.

Rejection Under 35 U.S.C. § 112, Second Paragraph

In the present Office Action at pages 2-3, the Examiner has rejected claim 11 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting "an acid salt" in the first line, for lack of antecedent basis. By the foregoing amendments, claim 11 has been amended to delete this recitation. Accordingly, this rejection has been fully accommodated; reconsideration and withdrawal are respectfully requested.

Rejection Under 35 U.S.C. § 103

In the present Office Action at pages 3-5, the Examiner has rejected claims 1-18, 21, 22, 23, 26-28 and 30-36 under 35 U.S.C. § 103(a) as allegedly being Rewinkel *et al.*, *Curr. Pharm. Design* 5:1043-1075 (1999) (hereinafter "Rewinkel"), in view of Nanteuil *et al.* (U.S. Patent No. 5,814,622; hereinafter "Nanteuil") and in further view of Adams *et al.* (U.S. Patent No. 5,780,454; hereinafter "Adams"). Applicants respectfully traverse this rejection.

Briefly, the Examiner asserts (1) that Rewinkel discloses a boronic acid having a methoxyalkyl substituent for R9 in present claim 1, a proline as recited in claim 17, a hydrophobic moiety in the form of a diphenylalanine residue, and a protected N-terminal amine group, along with a Ki for thrombin inhibition of 14 nM which is below 100 nM as recited in present claims 7 and 28; and (2) that Nanteuil discloses organoboronic acids and pharmaceutically acceptable salts thereof, including base and acid addition salts, as well as Na+, K+ and amines as examples of counterions for base addition salts. Therefore, according to the Examiner, it would have been *prima facie* obvious for one of ordinary skill to have taken the organoboronic acid compounds of Rewinkel, and modify

them in view of the disclosure of Adams by creating pharmaceutically acceptable salts thereof to produce the presently claimed compounds and compositions. Applicants respectfully disagree with these conclusions and the reasoning upon which they are based.

To establish a *prima facie* case of obviousness, the prior art must teach or suggest each and every element of the claimed invention. Additionally, there must be some suggestion or motivation, either in the prior art itself or in the knowledge generally available to one of ordinary skill in the art, to modify the prior art or combine the teachings of the prior art in the matter posited by the Examiner. *See, e.g.*, *In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2006); *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were allegedly known in the art at the time the invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

> However, a reference that teaches away from a given combination may negate a motivation to modify the prior art to meet the claimed invention. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."

Ormco Corp. v. Align Technology, Inc., 05-1426, Slip op. at 13 (Fed. Cir. Aug. 30, 2006) (quoting *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)).

The Examiner asserts that it would have been obvious "to form salts from known acids." *See* the present Office Action at page 4, third full paragraph. Applicants respectfully disagree, and submit that one of ordinary skill in the art would have had no motivation to make a base addition salt form of an organoboronate compound disclosed in Rewinkel. In fact, the person of ordinary skill in the art would have been *taught away* from making such a dosage form.

In making this rejection, the Examiner appears to assume that organoboronic acid compounds resemble and therefore would behave like other organic acid compounds, such as carboxylic acids. This is simply incorrect -- as one of ordinary skill would readily understand, unlike carboxylates, organoboronic acid compounds are known to be unstable as free acids. For example, Intl. Patent Appl. Publ. No. WO 02/059130 (hereinafter "*Gupta*"; of record in the present application) discloses that alkylboronic acids are relatively difficult to obtain in analytically pure form, that they readily form boroxines (anhydrides) under dehydrating conditions, and that they are often air-sensitive, *e.g.*, to oxidation; and concludes that "[t]hese difficulties limit the pharmaceutical utility of boronic acid compounds." *Gupta*, at ¶ [0004]. Similarly, S. Wu *et al.*, *J. Pharm. Sci.*, **2000**, *89*, 758-65 (hereinafter "*Wu*"; of record in the present application) reports that:

> During an effort to formulate 2-Pyz-(CO)-Phe-Leu-$B(OH)_2$ for parenteral administration, the compound showed erratic stability behavior and was quite unstable in certain solvents.

Wu, at 758, right-hand column. *See also* the present Specification, at page 4, lines 24-27; page 4, line 35 through page 5, line 2; and page 5, lines 4-7.

Aware of the instability of boronic acids and of the "erratic stability behavior" of organoboronates such as a peptide boronic acid during attempts to formulate it for pharmaceutical uses, a person of ordinary skill, upon reading the references, would be led in a direction "divergent from the path that was taken by the Applicants." Recognizing the "need in the art for improved formulations of boronic acid compounds," *Gupta* reports that "lyophilization of an aqueous mixture comprising a boronic compound and a compound having at least two hydroxyl groups produces a stable composition that readily releases the boronic acid compound upon dissolution in aqueous media." *Gupta*, at ¶ [0005]. Thus, *Gupta* discloses solving the stability problem by formulating the boronic acid as a lyophilizate with another compound, *e.g.*, a sugar, which lyophilizate can be reconstituted with an aqueous solvent such as saline for administration. The lyophilisate was found to produce a mass spectrum signal indicative of the formation of a "covalent ester adduct". *Gupta*, at ¶¶ [0136], [0141], [0144], the ester adduct being illustrated at ¶ [0070]. *See also* the present Specification, at page 5, lines 4-18.

In a similar vein, V. Martichonok and J.B. Jones, *J. Am. Chem. Soc.*, **1996**, *118*, 950-58 (hereinafter "*Martichonok*"; of record in the present application) discloses formation of the corresponding diethanolamine ester to impart stability to boronic acids. *See Martichonok*, at 951, right-hand column ("this derivatization also provided protection against possible autoxidation of the acetamido boronic acids [] by atmospheric oxygen"). Similarly, D.S. Matteson *et al.*, U.S. Patent No. 5,681,978 (hereinafter "*Matteson*"; of record in the present application), discloses oxidative resistance of the

pinacol ester of a boronic acid. *Matteson*, at column 4, lines 57-67. *See also* the present Specification, at page 4, lines 29-33.

Indeed, in making this rejection by relying in part on the disclosure of Adams, the Examiner apparently believes that Adams would have motivated one of ordinary skill to make salts of organoboronic acids. This conclusion is not supported in Adams, since Adams concerns the boronic acid drug bortezomib (Velcade®) -- compound MG-341 on cols 59-60 of Adams -- and yet it was found that stabilization of Velcade® required *esterification* of the organoboronate as indicated in Wu and Gupta (*see also* the package insert for Velcade®, attached hereto as Appendix A, which confirms that this compound is marketed as a mannitol *ester*; *see* Appendix A at page 1, lines 10-12).

Furthermore, Applicants have conducted stability testing of one embodiment (referred to as "TRI 50c") of the presently claimed compound, in the free acid and sodium salt forms. A summary of the results of these studies is attached hereto as Appendix B. What these data show is that a sample of TRI 50c in the free acid form at 25°C and 60% relative humidity reduced from a 50c content of 97.18% to just 58.83% within three months (Table 2 of Appendix B). In contrast, a sample of a sodium salt of TRI 50c under the same conditions was at 95.3% after 3 months. Moreover, there was significant morphological degradation observed in the free acid form of this compound over time, as depicted in Table 1 and Figure 7.1 in Appendix B. These results confirm the observations reported in Examples 27 and 28 of the present application, and the calcium salt stability data reported in the 1st Table of Example 13 of commonly owned U.S. Patent No. 7,112,572.

The Examiner's reliance (at page 4 of the present Office Action) on Davies *et al.* (*Pharm. J. 266*:322-323 (2001) is also misplaced. With respect to stability, at best Davies only discloses that polar ionic groups create a hydrophilic environment which can reduce stability (*see, e.g.*, Davies at ¶1 under the heading "Stability"). As noted above, however, Wu discloses that boropeptides are unstable, including in various aqueous media (*see, e.g.*, Wu at page 759, left hand side), while salts are generally known to enhance solubility (as confirmed, *e.g.*, by comparison of examples 10 and 25 of the present application), which in turn can reduce stability as disclosed by Davies *et al* .

Hence, in view of the cited references and information that was readily available in the art at the time, instead of being motivated to make the boronic acid salts of the presently claimed invention, one of ordinary skill would more likely have been taught *away* from making such revisions to the compounds disclosed in Rewinkel. That is, aware of both the problem with stability of boronic acids and two reported solutions to the problem, a person of ordinary skill in the art would not have been motivated to make the presently claimed invention but instead likely would have pursued one of the aforementioned solutions (*e.g.*, lyophilization in the presence of a sugar, or esterification). Therefore, there would have been no motivation for one of ordinary skill to have made and used the presently claimed compositions. Absent such motivation, the cited references may not be properly combined to render the claimed invention obvious. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988).

For at least the foregoing reasons, the cited references do not render claims 1-18, 21, 22, 23 26-28 and 30-36 *prima facie* obvious. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Double Patenting

The Examiner has rejected claims 1-23, 26-28 and 30-38 for non-statutory obviousness-type double patenting over claims 1-21, 23 and 25 of U.S. Patent No. 7,122,572 [sic]. Applicants note that it is presumed that there is a typographical error in this citation in the Office Action, and that this rejection was intended to be made over commonly owned U.S. Patent No. 7,112,572. In any event, Applicants respectfully request that this rejection be held in abeyance until the Examiner has identified allowable subject matter in the present application. At such time, Applicants will consider filing a terminal disclaimer to obviate this rejection.

Applicants also note that, citing copending U.S. Application Nos. 10/937, 854 and 11/078,097, the Examiner has invited Applicants to "review all subject matter considered the same or similar" in these cited applications that may "encompass[] the same or similar subject matter of the instant application," and to "submit the appropriate Terminal Disclaimer(s)." *See* the present office Action at page 6, third paragraph. Applicants respectfully decline this invitation, as the Examiner has made no obviousness type double-patenting rejection in the present matter over either the '854 application or the '097 application, nor over any other application present in "the continuity data" referred to by the Examiner. If the Examiner is inclined to raise such double patenting rejection(s) over these copending applications, Applicants will decide at that time whether or not to submit any terminal disclaimer(s) that may be necessary to obviate such rejection(s).

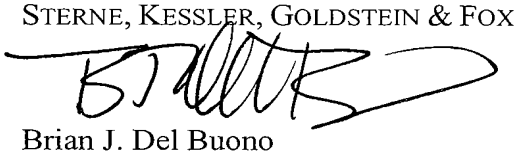
Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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